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Joan Claybrook, President

March 7, 2000

Jane Henney, M.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

**CITIZEN'S PETITION TO IMMEDIATELY REQUIRE CLASS LABELING FOR THE
DIABETES DRUGS TROGLITAZONE (REZULIN), ROSIGLITAZONE (AVANDIA) AND
PIOGLITAZONE (ACTOS)**

Dear Dr. Henney:

Public Citizen, a nationwide consumer organization, with a membership of more than 150,000, hereby petitions the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug and Cosmetic Act 21 U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30 to immediately require revision of the inadequate, misleading, and potentially dangerous professional product labeling for the thiazolidinediones or "glitazone" diabetes drugs: troglitazone (Rezulin), rosiglitazone (Avandia), and pioglitazone (Actos). The glitazone drugs are approved as adjuncts to diet and exercise to improve blood sugar control in patients with type 2 diabetes. However, their labels are inadequate and fail to mention or explain some important safety and efficacy information that appear to be class effects which apply to all three drugs in this class. Class efficacy issues include the lack of efficacy compared to previously available drugs, sulfonylureas, and the deterioration of blood sugar levels when patients are switched from other oral anti-diabetic drugs to the glitazones. Safety issues include liver toxicity, effects on heart function, weight gain, edema, anemia, low blood pressure, elevated lipid levels, and possible changes in progesterone levels.

The first member of the group to be approved, troglitazone (Rezulin), is a drug that has been shown to be too dangerous to be used safely because of its liver toxicity. It should be banned, as requested in our July 27, 1998 petition to the FDA (it has already been withdrawn in Great Britain). Although the severity of the risks due to liver failure do not justify the continued marketing of troglitazone, as long as it remains on the market in the U.S., we include it in our requests for changes in the labeling of the other glitazone drugs.

Ralph Nader, Founder

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This petition is based on reviews by FDA Medical Officers, Statisticians, and Pharmacologists as well as transcripts of FDA advisory committee meetings, and a review of the scientific literature for troglitazone, rosiglitazone, and pioglitazone. We compared this information to the current professional product labeling and found that much of this information was never included in the label, or seriously understated. As a result, the labeling omits important safety and efficacy information to such an extent that physicians are likely to prescribe these drugs inappropriately.

There is no direct evidence that lowering glucose or HbA1c levels with one of the glitazone drugs reduces the risks of microvascular or macrovascular disease or mortality in patients with type 2 diabetes. In contrast, there is some evidence that other oral hypoglycemics do succeed in doing so.¹ It is, therefore, especially important that the drugs in this class not increase the rate of adverse events lest they supplant the use of drugs with superior efficacy track records.

This petition also strongly urges the FDA to require mandatory distribution by pharmacists of scientifically accurate information, written in non-technical language, for consumers in the form of FDA-approved Medication Guides with each new and refill prescription for these drugs.

Our review of the published and unpublished data revealed the following efficacy concerns:

- Both hemoglobin A1c (HbA1c)² and blood sugar levels deteriorate when patients on other types of oral anti-diabetic drugs are switched to troglitazone, rosiglitazone, or pioglitazone and rarely return to the levels seen before glitazone treatment began (before/after trials).
- Glitazones are not as effective (and appear to be less safe) than the older sulfonylurea class of drugs such as glyburide (Micronase) in reducing blood sugar and hemoglobin A1c (head-to-head comparisons).³

1 UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes: UKPDS 33. The Lancet 1998;352:837-853.

2 HbA1c is an indicator of blood sugar control over the preceding two to three months.

3 Medical Officers' Reviews for glitazones.

Our review of the data revealed the following safety concerns:

- **Liver Toxicity:** Drug-induced liver failures with troglitazone led to its withdrawal from the market in Great Britain. Liver failures have also been reported to the FDA in patients taking troglitazone and rosiglitazone. For troglitazone, as of March 1999, there were 43 reports of acute liver failure in the U.S. with 28 known deaths.⁴ For rosiglitazone, there were four cases of liver failure and 13 cases of ALT elevations (a measure of liver damage) reported to the FDA in the first four months of marketing.⁵ More recently, two case reports of serious hepatocellular injury attributed to rosiglitazone have been reported in the medical literature.^{6,7}
- **Heart Function:** Cardiac effects were the most consistent toxicity finding in studies in rats, mice, and dogs. Effects on the heart included increased size and weight, atrial thrombosis, and fluid accumulation around the lungs. Heart "dysfunction" was listed as a cause of death in rats on rosiglitazone. Heart failure has been reported to the FDA for troglitazone at a much higher rate than for Glucotrol (glipizide), an older diabetes drug from the sulfonylurea class (56 cases of heart failure in the first 19 months of use for troglitazone vs. 4 cases after 13 years of Glucotrol use).⁸
- **Weight Gain (as fat):** The first step in the action of the glitazones is to bind to a protein in the nucleus, the peroxisomal proliferator-activator receptor gamma (PPAR γ).⁹ Binding triggers the transcription of a set of genes leading eventually to the production of more fat cells.¹⁰ These fat cells increase their uptake of glucose

4 Advisory Committee on Troglitazone; March 26, 1999.

5 Adverse Events reported to FDA (AERS reports) as of October 7, 1999.

6 Al-Salman J, Arjomand H, Kemp DG, et al. Hepatocellular injury in a patient receiving rosiglitazone. *Annals of Internal Medicine* 2000;132:121-124.

7 Forman LM, Simmons DA, Diamond RH. Hepatic failure in a patient taking rosiglitazone. *Annals of Internal Medicine* 2000;132:118-121.

8 AERS data for Glucotrol (www.fda.gov/cder/adr/index.htm); AERS data for troglitazone as of 10/07/99.

9 Young PW, Buckle DR, Cantello BCC, et al. Identification of high-affinity binding sites for the insulin sensitizer rosiglitazone (BRL-49653) in rodent and human adipocytes using a radioiodinated ligand for peroxisomal proliferator-activated receptor gamma. *Journal of Pharmacology and Experimental Therapeutics* 1998;284:751-759.

10 Lehmann JM, Moore LB, Smith-Oliver TA, et al. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR γ). *The Journal of Biological Chemistry* 1995; 270:12953-12956.

from the blood and convert this glucose into fat. FDA does not list weight gain as an adverse event since it is considered an 'essential' part of the way these drugs work.¹¹ Patients can expect a weight gain of up to 5% of body weight.

- **Edema:** Thiazolidinediones block the calcium channels in the small arteries (arterioles). These are the same channels blocked by a class of widely used high blood pressure drugs called "calcium antagonists" or "calcium channel blockers". The decrease in arteriolar resistance leads to fluid filtration from blood to tissue. Fluid accumulation may occur peripherally or in the lungs, leading to both peripheral and pulmonary edema. Significant body weight increases may result from fluid accumulation, a second mechanism of weight gain in people taking these drugs.
- **Anemia:** When glitazones bind to PPAR γ receptors in bone marrow cells, they cause the production of more fat cells there, as they do in other tissues. As the fat cells become more numerous, they compress the other bone marrow cells and can cause a decrease in their ability to produce red blood cells and, hence, anemia. The formation of white blood cells can also be decreased by the same mechanism. Eight patients in monotherapy studies (0.3%) were withdrawn from rosiglitazone because of anemia compared to no patients on metformin, sulfonylurea, or placebo.¹² Five patients (0.8%) on pioglitazone had decreases of >10%.¹³
- **Low Blood Pressure:** Glitazones bind to and inhibit the same calcium channels as the calcium channel blockers and with the same result: the lowering of blood pressure. Statistically significant decreases in diastolic blood pressure (average decrease of -6.5 mm) were seen in patients on troglitazone, the only drug of the three where this was routinely measured.¹⁴
- **Increased Cholesterol Levels:** Higher cholesterol levels are potentially damaging to cardiovascular health. They are seen to some extent with all the glitazones but most prominently with rosiglitazone (statistically significant increases in LDL and total

11 Advisory Committee for Pioglitazone; April 23, 1999.

12 Medical Officer's Review of Rosiglitazone; April 6, 1999; p.34.

13 Medical Officer's Review of Pioglitazone; June 23, 1999; p.40.

14 Ghazzi MN, Perez JE, Antonucci TK, et al. Cardiac and glycemic benefits of troglitazone treatment in NIDDM. Diabetes 1997;46:433-439.

cholesterol).¹⁵ Increases in LDL ranged from 18% to 33% depending on change from baseline in HbA1c.¹⁶

I. EFFICACY CONCERNS

There were two types of studies looking at HbA1c levels (a measure of glucose control) in glitazone-treated patients: 1) HbA1c levels in patients switched from other diabetes drugs ("before") to a glitazone ("after") (before/after trials) and 2) HbA1c levels in head-to-head comparisons between a glitazone and another anti-diabetic drug. A few trials combined both approaches. The following section examines the before/after trials.

IA. GLITAZONES ARE LESS EFFECTIVE AS MONOTHERAPY IN DIABETIC PATIENTS PREVIOUSLY TREATED WITH AN ORAL ANTI-DIABETIC DRUG FROM ANOTHER CLASS (see p. 31 of Appendix for current Label)

The current labels include only one or two understated sentences on the deterioration of glycemic control in patients switched to a glitazone from other oral anti-diabetic drugs. Some information is included under "clinical studies" but needs to be expanded, explained more clearly, and be more easily accessible; we have included figures that clearly demonstrate this effect (Figs. 1-3, pp. 8-10 and Figs. 5-9, Appendix). HbA1c levels are shown as they changed during the course of the clinical trials (all figures are taken from FDA reviews).

In these studies, patients who were previously on a non-glitazone oral anti-diabetic drug (or drugs) were removed from them for a period of 3 to 8 weeks before the trial started; those who were being treated with diet alone continued on that regimen. Then at time zero on the figures, patients were assigned on a randomized basis to dosing with a glitazone or placebo. Patients' HbA1c levels were then followed over time, usually for six months. In this section, we compare the patients' HbA1c levels on the other oral drug to those on the glitazone.

As glitazone dosing began, a dramatic difference in HbA1c levels emerged between those who had been on diet only [Figs 1a (troglitazone), 2a (rosiglitazone), and 3a (pioglitazone)] and those who had previously been on another oral anti-diabetic drug (Figs 1b, 2b, and 3b) at the end of the 6-month follow-up. Those who had previously been on diet only, either maintained their baseline HbA1c level or had that level fall

¹⁵ Statistical Review of Rosiglitazone; May 11, 1999; p.27.

¹⁶ Ibid; p.49.

(these decreases in HbA1c were generally 0.5 to 1%, a relatively minor improvement.) Conversely, in those who had previously been on another oral anti-diabetic treatment, HbA1c levels never returned to the levels achieved with their previous therapy.

Evidence Supporting Labeling Change

Troglitazone: There were two studies of before/after design (#032 and #031). In #032, the Troglitazone Study Group (the group of clinicians that performed the trials with troglitazone) defined two distinct groups of patients based on prestudy therapy (those on diet and exercise only vs. those on a sulfonylurea). It is clear from Fig 1b, p.8 that patients previously on an oral agent (usually a sulfonylurea) experience an average HbA1c increase of at least 1% over the 6 month study period compared to their previous agent.¹⁷ There were similar results in Study #031 where the troglitazone-treated patients' HbA1c's had not returned to their levels with the previous agent after 12 weeks (Fig. 4, Appendix).

Rosiglitazone: Three studies of this design have been done for rosiglitazone. In the first (study #011, Fig.2, p.9), the patients had not returned to the HbA1c level achieved with the previous agent even after 6 months of rosiglitazone treatment. There were similar findings in study #024 ; HbA1c levels generally remained 1% above baseline after six months (Fig. 7, Appendix). In study #020, HbA1c levels also increased slightly on rosiglitazone compared to previous therapy, but the change was less than in studies #011 and #024.

The label for rosiglitazone under "Clinical Studies" acknowledges that "For many previously-treated patients, HbA1c and free blood glucose (FBG) had not returned to screening levels by the end of the study". However, this critical information appears only in the obscure "Clinical Studies" section of the label.

Pioglitazone: Three studies of this design (#001, #012, and #026; Figs. 3, 8, and 9) have been done for pioglitazone, and all had the same finding. Patients previously on another oral agent generally had HbA1c levels at least 1% higher than at baseline at the end of the study period (16-26 weeks). However, important comments by the FDA Medical Officer reflecting these striking data never made it into the label. For example,

¹⁷ Fonseca VA, Valiquett TR, Huang SM, et al. Troglitazone monotherapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized controlled study. *Journal of Clinical Endocrinology and Metabolism* 1998;83:3169-3176.

he stated that in patients withdrawn from previous antidiabetic medication, "it is clear that HbA1c levels rose in all groups". He added, "... PIO appears to be inferior to patients' previous antidiabetic medication. Since patients' hyperglycemia deteriorates when they are switched to PIO from other medications, it is hard to see how these data can be used to support an indication of initial monotherapy. This is the same problem we faced with troglitazone. . . ".¹⁸ (Fig. 3, p. 10 and Figs. 8 & 9, Appendix).

Possible Drug Misuse by Formularies Because of Inadequate Labeling: Misuse is an inevitable consequence of lack of information in the label. The manufacturer of rosiglitazone estimates that one-third of patients using the drug were switched from other therapies.¹⁹ Thus, according to the evidence referred to above, they are likely to experience diminished blood sugar control.

¹⁸ Medical Officer's Review of Pioglitazone; June 23, 1999; p.4.

¹⁹ Avandia 90% formulary acceptance achieved at one month post-launch-SB .The Pink Sheet; September 27, 1999; p. 23.

Figure 1a TROGLITAZONE Study #032

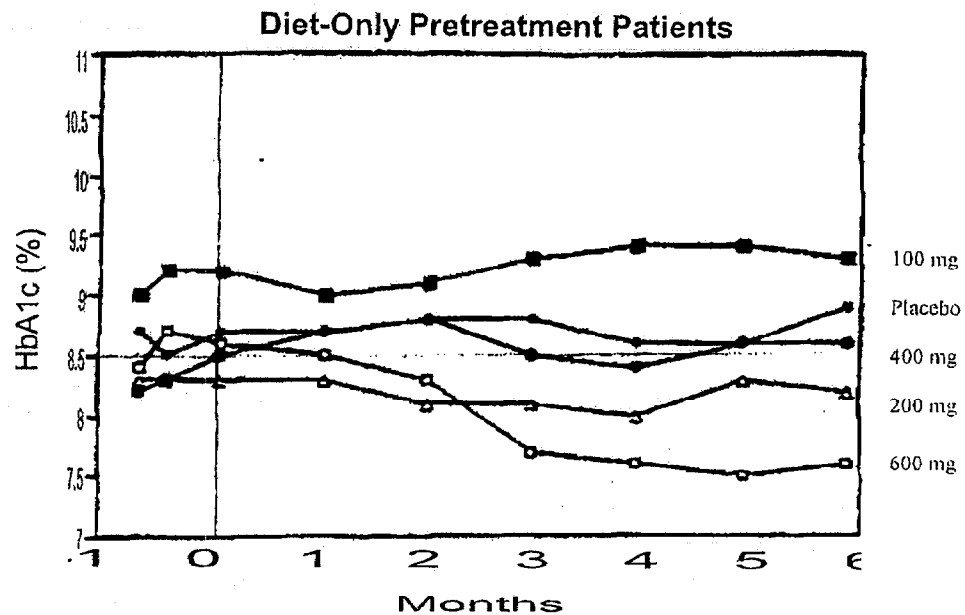


Figure 1b TROGLITAZONE Study #032

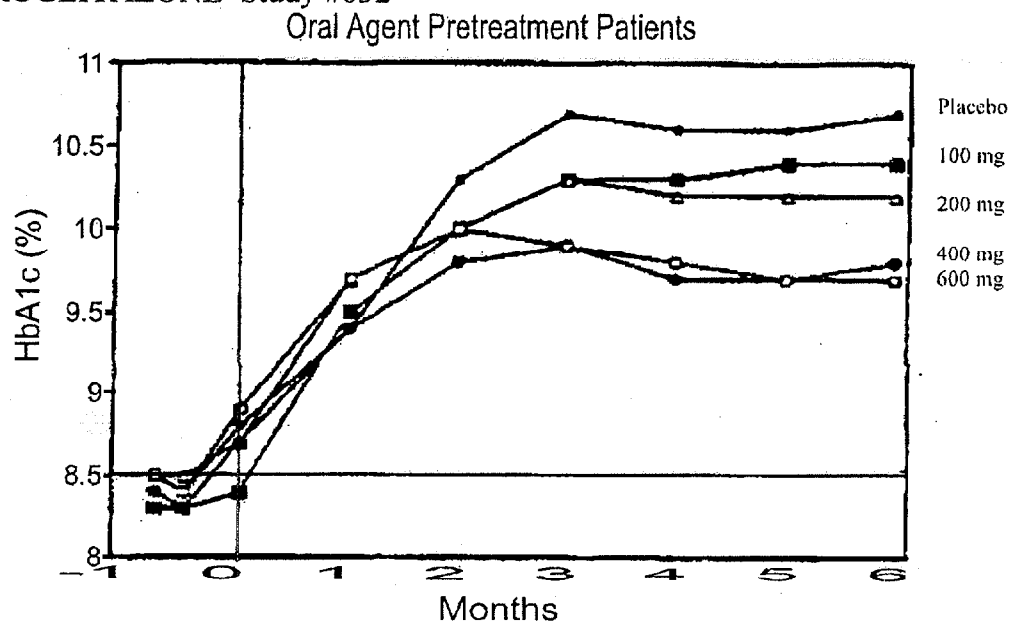


Figure 2 ROSIGLITAZONE Study #011

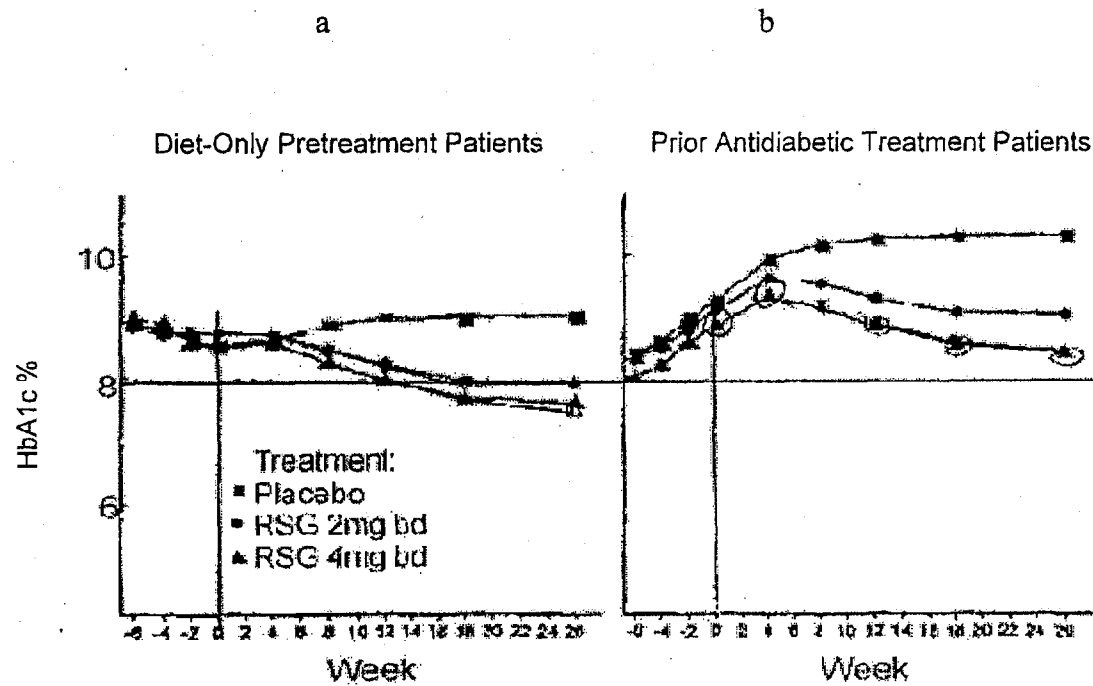


Figure 3a PIOGLITAZONE Study #001

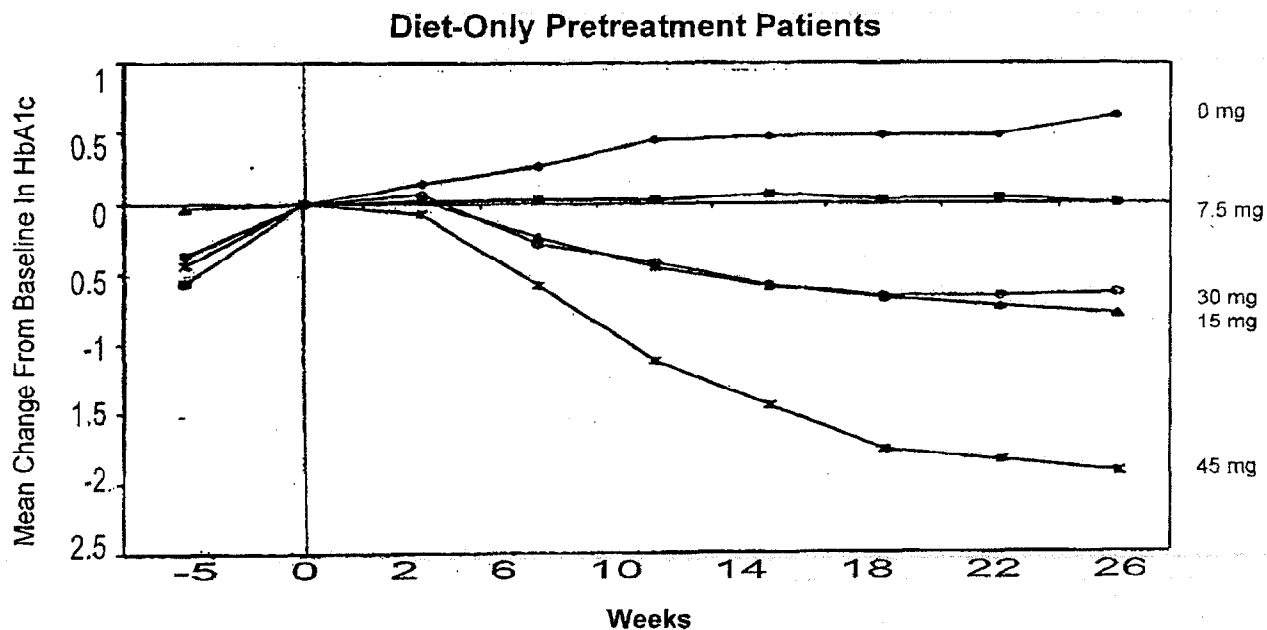
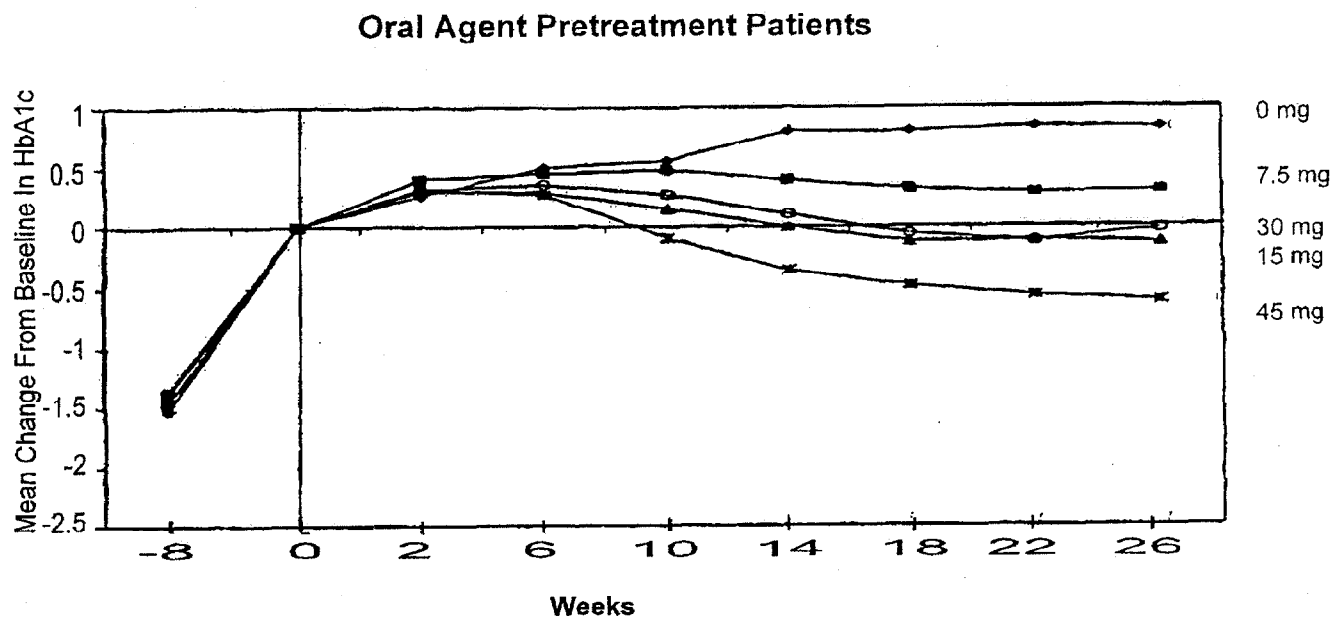


Figure 3b PIOGLITAZONE Study #001



IB. GLITAZONES, WHEN USED ALONE, ARE NOT AS EFFECTIVE AS OLDER SULFONYLUREAS IN REDUCING BLOOD SUGAR AND HbA1c IN HEAD TO HEAD TRIALS

Current Glitazone Labeling: There is no comparative information in the troglitazone and pioglitazone labels and little information on the rosiglitazone label (see p. 31 of Appendix and below).

Evidence Supporting a Labeling Change for Efficacy (head-to-head trials)

Troglitazone: Two phase III studies put patients on troglitazone, glyburide (a sulfonylurea), or both together (#042 and #055).

Study #042: The FDA Medical Officer noted the large number of withdrawals from the 48-week study: 23% of troglitazone patients withdrew for lack of efficacy (vs. 4% of glyburide-treated patients). Overall, withdrawals were 40% for troglitazone patients vs. 12% in the glyburide group.²⁰

Study #055: The lack of efficacy was the most common reason for failure to complete the study for patients on troglitazone: drop-outs due to lack of efficacy were 44% for patients on 600 mg troglitazone compared to 25% for those on glyburide (Fig. 5, Appendix).²¹ The Medical Officer commented that, "The study also shows that patients on glyburide who are switched to troglitazone can expect to experience a deterioration in glycemic control."²²

Rosiglitazone (RSG): Study #020 (Fig. 6 Appendix) was a combination of a head-to-head trial with before and after comparison. While at first glance the results of #020 appear less dramatic, the statistical review still found that at the 2 or 4 mg bid dose of rosiglitazone even after one year, "The results for the 2 mg [bid] dose [of rosiglitazone] are significantly worse than glibenclamide [glyburide] on the primary efficacy measure" and "The results are borderline [effective] for the RSG 4 mg BID dose compared to glibenclamide . . .".²³ Physicians in the study were not allowed to increase doses of glyburide after week 12, even if lack of efficacy indicated an increase was needed, so

20 Medical Officer's Review of Troglitazone NDA; January 17, 1997; p.43.

21 Medical Officer's Review of Troglitazone NDA; July 3, 1997; p.4.

22 *ibid*; p.7.

23 Statistical Review of Rosiglitazone NDA; May 11, 1999; p.26.

that glyburide doses may not have been optimal, making rosiglitazone appear better by comparison. Withdrawals due to lack of efficacy were higher with rosiglitazone: 3.4% (glibenclamide), 11% (2 mg bid rosiglitazone), and 8% (4 mg bid rosiglitazone).²⁴

Pioglitazone: There were no head-to-head studies with pioglitazone.

SUMMARY: Of these ten studies using 3 drugs of the same therapeutic class, nine out of ten showed less efficacy with the glitazone, tested either head-to-head with a sulfonylurea or when patients were switched from a sulfonylurea to a glitazone.

We acknowledge that the before-after study design has some weaknesses. In particular, it is possible that those who began the study on a non-glitazone anti-diabetes drug were subject to selection bias. They may be patients for whom the effectiveness of the non-glitazone drug was relatively high, toxicity relatively low, and compliance relatively high. It might be expected that such patients would do worse even on an approximately equally efficacious anti-diabetes drug. However, we are struck by the similar findings from the head-to-head trials, which are not subject to this selection bias. Consequently, we consider the data from the before-after trials to provide support for the more definitive results from the head-to-head comparisons.

Moreover, the worsening of HbA1c levels, in patients who were on a sulfonylurea and were subsequently switched to a glitazone, was seen across all three drugs in the class. Patients actually experienced decreased glycemic control when they were removed from other oral anti-diabetic medication(s) and placed on any one of the three approved glitazones (troglitazone, rosiglitazone, or pioglitazone): both blood free glucose and hemaglobin A1c began to rise such that after four to six months of treatment, patients were in poorer glucose control than when they began (Figs.1-3, pp.8-10 and Figs.4-9, Appendix).²⁵ Glitazones had higher drop-out rates due to lack of efficacy.

Suggested Professional Labeling Under Indications and Usage:

"In view of the relative lack of efficacy compared to the sulfonylureas, the known safety concerns, and the undefined hazards, the glitazones should not be first line agents.

²⁴ Medical Officer's Review of Rosiglitazone; April 16, 1999; p.13.

²⁵ Medical Officers' and Statisticians' Reviews for Troglitazone, Rosiglitazone, and Pioglitazone.

Sulfonylureas appear to produce better glycemic control with fewer adverse effects."

Suggested Patient Labeling (Medication Guide): Since [Drug] may not work as well as sulfonylureas, one of these should be tried first.

II. SAFETY CONCERNS

IIA. LIVER TOXICITY (See p. 32 of Appendix for current labeling)

Evidence Supporting Labeling Change

Troglitazone: In December 1997, based on 130 worldwide cases of liver damage linked to troglitazone, including six deaths, the British government concluded that "the risks of troglitazone therapy outweigh the potential benefits" and the drug was withdrawn from the market there. The British government added that "at present, no clear risk factors for the development of hepatic reactions have been identified which might allow the drug to be used safely in some patients."²⁶ Glaxo-Wellcome, which had been marketing the drug in the UK, also withdrew license applications for troglitazone²⁷ under the European Commission's "mutual recognition" process. Despite our July 27, 1998 petition to ban the drug in the U.S.²⁸, the drug remains on the market, although its indication as monotherapy has been withdrawn.²⁹

Rosiglitazone: Evidence of liver toxicity seen in the clinical trials included eleven patients on rosiglitazone who had an increase in ALT of >3x the upper limit of normal (ULN), five of whom had to be withdrawn from treatment.³⁰ The Medical Officer noted: "Although there were no cases of 'fulminant hepatitis' attributed to RSG [rosiglitazone], there was one patient with a reversible elevation in ALT of 19x ULN. There was also a case of jaundice attributed to hepatitis A but [without] the documentation." He continued, "I am concerned that long-term exposure to RSG may give rise to a similar liver problem as with troglitazone but with a time lag reflecting the lower dose."³¹ The Committee for Proprietary Medicinal Products (European regulators) has voted to reject

²⁶ Committee on Safety of Medicines. Troglitazone (Romozin) withdrawn. *Current Problems in Pharmacovigilance* 1997;23:13.

²⁷ Troglitazone suspended in U.K. after more adverse events. *Scrip*, December 5, 1997; No.2290; p.15.

²⁸ Public Citizen petition to FDA; July 27, 1998; www.citizen.org/hrg/PUBLICATIONS/drugs.htm.

²⁹ FDA Talk Paper; New labeling and use changes for rezulin. June 16, 1999. (www.fda.gov/opacom/Answers.html).

³⁰ Medical Officer's Review of Rosiglitazone; April 16, 1999; p.32.

³¹ Ibid; p.41

the application for rosiglitazone.³²

Adverse hepatic events reported to the FDA between when rosiglitazone was launched (June 1999) and October 1999 included four cases of hepatic failure and 13 cases of ALT elevations.³³ Hepatocellular vacuolation was seen in mice and ALT increases of up to 12-fold were seen in dogs³⁴ and 9-fold in rats³⁵. Two recent reports have been published: one of hepatocellular injury and one of hepatic failure in patients taking rosiglitazone for 2 and 3 weeks, respectively.^{36,37} None of this information concerning liver toxicity of rosiglitazone is present in the current labeling.

Pioglitazone: In the U.S. trials, there were 9 patients on pioglitazone with drug-related ALT values >3x ULN compared with only 2 patients on placebo, according to the Medical Officer's review.³⁸ In addition, there were 12 pioglitazone patients (and only one placebo patient) hospitalized for acute cholecystitis.

SUMMARY: Elevations of ALT reflecting liver toxicity were seen across the class. The two drugs that have been marketed long enough to provide additional data (troglitazone and rosiglitazone) have caused liver failure leading to transplantation or death.

Suggested Professional Labeling for Liver Toxicity

Troglitazone: The label has a black box warning as well as a medication guide for patients.

Rosiglitazone and Pioglitazone (Add to current label): Troglitazone-like hepatitis remains a major safety concern for this class of drugs. For rosiglitazone, there have been four cases of hepatic failure reported to the FDA between the June 14, 1999 launch and October 7, 1999.³⁹ Recently, two reports (one hepatocellular injury and one

32 Avandia held up at 1st EU hurdle. Scrip October 27, 1999; No.2484, p.21.

33 AERS report from FDA as of 10/07/99.

34 Pharmacology Review of Rosiglitazone; May 11, 1999; pp.35 & 18.

35 Pharmacology Review of Rosiglitazone; July 10, 1996; appendix Table 9.

36 Al-Salman J, Arjomand H, Kemp DG, et al. Hepatocellular injury in a patient receiving rosiglitazone. Annals of Internal Medicine 2000;132:121-124.

37 Forman LM, Simmons DA, Diamond RH. Hepatic failure in a patient taking rosiglitazone. Annals of Internal Medicine 2000;132:118-121.

38 Medical Officer's Review of Pioglitazone; June 23, 1999; p.37.

39 AERS report from FDA as of 10/07/99.

hepatic failure) have appeared in the medical literature. For pioglitazone, there were 9 cases of drug-related ALT elevations vs. 2 on placebo in the clinical trials. Twelve pioglitazone patients and one placebo patient were hospitalized for acute cholecystitis in these trials.

Suggested Patient Labeling (Medication Guide for rosiglitazone and pioglitazone) [Drug] has been shown to cause damage to the liver; some patients have suffered liver failure. Your doctor will test your blood before you start taking [drug] to see if your liver is normal. This test should be repeated every two months during your first year of therapy to see if [drug] is adversely affecting your liver. Additional tests may be needed to follow up on abnormal results. (Patient information similar to that in the Rezulin label should be added as well.)

IIB. EFFECTS ON THE HEART (See p. 33 of Appendix for current labeling)

The potential deleterious effects on heart function are downplayed in the current label.

Evidence Supporting Labeling Change **ANIMAL STUDIES**

Troglitazone: The pharmacology reviewer suggested that drug-induced cardiac hypertrophy and myocardial degeneration contributed to the high mortality rate in rats⁴⁰; in mice, heart weights were increased, and there was epicarditis with fibrosis as well as periarteritis.⁴¹

Rosiglitazone: Cardiac effects in rats, mice, and dogs included increased heart weights and atrial thrombosis. Heart rates were increased in dogs; fluid was seen in the pericardial sac of dogs while pulmonary thrombosis was stated to be a cause of death in rats.⁴² The pharmacologist added that, "The severe cardiopulmonary action of this drug appears to be related to the drug exposure duration rather than the dose", increasing the likelihood that cardiac problems may increase with increasing duration of use.

Pioglitazone: In rats, pioglitazone caused death from heart dysfunction: there was

40 Pharmacology Review of Troglitazone; January 9, 1997; pp.16, 29, 34

41 Ibid; p.26.

42 Pharmacology Review of Rosiglitazone; May 11, 1999; pp.17, 20-23, 25, 35, 40-42.

hypertrophy of atrial musculature and thrombosis in the atrium. Fluid accumulated in the thoracic, abdominal, and pericardial cavities. Cardiomyopathy and cardiac dysfunction were present at only three times the human exposure. Irreversible effects in rats and dogs included cardiomyopathy, thoracic cavity fluid, bilateral atrial hypertrophy, and increased lung weight. ST segment depression was seen in dogs.⁴³

Evidence Supporting Labeling Change

HUMAN STUDIES

Troglitazone: The Troglitazone Study Group published findings on 154 diabetics in an open-label study on cardiac function. They postulated that the statistically significant decrease in diastolic blood pressure and reduction in peripheral resistance could be due to calcium channel blocker activity. They worried that, "An increase in the sympathetic tone to compensate for the peripheral vasodilation and reduction in afterload would be a potential concern."⁴⁴ The Adverse Event Reporting System (AERS) of the FDA lists 56 cases of heart failure between November 1997 and June 1998. This can be compared with a sulfonylurea, glucotrol, with only 4 cases of heart failure reported over a period of 13 years (from approval in 1984 until 1997).⁴⁵

Rosiglitazone: In a summary of clinical trial data, acute myocardial infarctions occurred in 22 patients (0.5%) on rosiglitazone and was fatal in six, a result "higher than in other treatment arms". In the monotherapy trial (#011), chest pain was reported in 0.0% (placebo patients), 1.7% (patients on 2 mg bid rosiglitazone), and 3.3% (patients on 4 mg bid); Five patients on rosiglitazone had acute myocardial infarctions.⁴⁶

The Medical Officer's other concerns included increased cholesterol levels, electrocardiographic (EKG) changes, and chest pain. In addition, "There needs to be mention [in the label] of treatment emergent EKG changes [accelerated ventricular rhythms were seen in 2/16 healthy volunteers], chest pain, etc. . ."⁴⁷ This never occurred. The Medical Officer also felt that echocardiogram monitoring (the technique

43 Pharmacology Review of Pioglitazone; June 30, 1999; pp.16-18, 20, 38, 41.

44 Ghazzi MN, Perez JE, Antonucci TK et al. Cardiac and glycemic benefits of troglitazone treatment in NIDDM. Diabetes 1997;46:433-439.

45 Adverse Drug Reaction (ADR files) database from the FDA from late 1960's through January 1997; www.fda.gov/cder/adr/index.htm.

46 Medical Officer's Review of Avandia; April 16, 1999; p.28.

47 Ibid; p.40.

used in clinical trials) was not sensitive enough to detect small, but significant, changes. Only 28 patients in the rosiglitazone clinical trials had pre-existing congestive heart failure (types 1 or 2), a sample too small to allow conclusions as to rosiglitazone safety in that population.⁴⁸ The AERS already lists 5 cases of heart failure out of approximately 50 adverse events reported between June 14 and October 7, 1999, a further reason for increased caution.

Pioglitazone: The potential to cause cardiomegaly was anticipated from preclinical studies. For this reason, the sponsor performed a 26-week echocardiogram study in diabetics (those without valvular abnormalities, ischemic heart disease, or symptomatic heart failure). Four doses of pioglitazone were compared with placebo. The Medical Officer concluded that, "The results of this [echocardiogram] study provide little, if any reassurance that PIO [pioglitazone] does not damage the heart".⁴⁹ In the other clinical trials, the Medical Officer noted that five patients on pioglitazone had cardiomegaly on chest x-ray; he did not mention this finding as occurring in the comparator groups.⁵⁰

SUMMARY: In animal studies, toxic effects on heart structure and function were seen across all drugs in the class and were responsible for increased mortality in rats. Clinical trials excluded people most at risk and, in most studies, did not use methods that were sensitive enough to detect problems. The Medical Officer felt that the label should mention EKG changes and chest pain, but this did not happen. Even though there are accumulating reports of a large number of cases of heart failure in humans, information in the labels concerning cardiac toxicity is minimal.

Suggested Professional Labeling For Effects on the Heart

In animal studies, the major toxic effect of all the drugs in the glitazone class was on the heart: cardiac hypertrophy and dysfunction were thought to have been a cause of death in rats (myocardial degeneration, fluid accumulation, and atrial thrombi). Studies in people have not been sensitive enough to rule out cardiac problems related to [drug].

Postmarketing adverse event data have included approximately 56 cases of heart failure in patients taking troglitazone (over an 18 month period) and 5 cases of heart failure in patients taking rosiglitazone (over four months) vs. 4 cases of heart failure for glucotrol, a sulfonylurea monitored for over a period of 13 years (from approval in 1984

48 Advisory Committee on Rosiglitazone; April 22, 1999.

49 Medical Officer's Review of Pioglitazone; June 23, 1999; pp.41-42.

50 Ibid; p.41.

until 1997).

Suggested Patient Labeling (Medication Guide)

Information from studies in rats, mice, and dogs has indicated that the heart can be harmed by exposure to [drug]. Although studies in people have generally been too small to detect a significant effect upon the heart, now that the drug is marketed, there have been considerably more reports of heart failure in patients using troglitazone than in patients using an older sulfonylurea, glucotrol. If you have a heart problem, your doctor may need to monitor your heart more frequently and be sure that the combination of [drug] with other drugs you are taking does not cause you harm.

II.C. WEIGHT GAIN (glucose conversion into fat)

(See p. 33 of Appendix for current labeling)

Weight gain has been a consistent finding with all the glitazones, ranging between an average of 2 and 12 pounds in particular studies, although some individuals have gained 5% of their body weight. Yet, there is no mention of weight gain in the troglitazone label and the information presented in the rosiglitazone and pioglitazone labels is buried in "Pharmacodynamics and Clinical Effects". Physicians and patients need to be aware of the likelihood of weight gain with the amount clearly stated as "pounds", not only as "kg".

Evidence Supporting A Labeling Change For Weight Gain

Troglitazone: The Medical Officer objected to the lack of data in the label on body weight gain in patients taking troglitazone, "This is not acceptable . . .".⁵¹

Rosiglitazone: The Medical Officer stated that "Patients treated with RSG [rosiglitazone] manifest undesirable changes in weight. . . [which] need to be discussed somewhere in the label."⁵² He added that this should include the fact that, "As an 'insulin sensitizer', RSG appears to lower glucose levels by converting glucose to fat."⁵³ The Medical Team Leader was also concerned about the increase in body weight: . . . "weight tended to continue to increase throughout the studies with no evidence of pause. The magnitude of weight increments was twice as much as those seen with

⁵¹ Medical Officer's Review of Troglitazone; July 3, 1997; p.31.

⁵² Medical Officer's Review for Avandia; April 16, 1999;p.40.

⁵³ Ibid; p.40.

sulfonylureas. . . . up to 5% of initial body weight in some studies."⁵⁴

Because of the weight gain, there are contradictory messages in the label: "Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient not only in the primary treatment of type 2 diabetes, but also in maintaining the efficacy of drug therapy" (underlining added). Yet, nowhere are patients told that they can expect to gain an average of 2 to 12 pounds (depending on the study and dose) as opposed to a weight loss on placebo.

Pioglitazone: The label has no information on weight gain for patients (see Appendix). At the Pioglitazone Advisory Committee meeting on adverse reactions, there was no discussion of weight gain since it was considered due to the drug's mechanism of action and not an adverse event.⁵⁵ The Medical Officer noted that improvement in hyperglycemia was associated with a weight gain, an average of 12 pounds, with no evidence of it reaching a plateau over time.⁵⁶ The same contradictory message regarding weight loss appears as in the rosiglitazone label..

SUMMARY: Body weight gain is a consistent finding across the class, ranging from 2 pounds to 5% of initial body weight, yet this information is either not present at all or not readily available in the current label.

Suggested Professional Labeling For Weight Gain

[Drug] of this class cause increases in body weight by the differentiation of preadipocytes to adipocytes coupled with the conversion of glucose to fat. Mean increases have ranged from 2 to 12 pounds in short term studies of 26 weeks; some individual increases could be much more. This weight gain did not plateau but continued throughout exposure to drug and could be as much as 5% of body weight. It is not known whether this fat accumulates in the abdomen (increasing cardiac risk) or elsewhere in the body. It is also not known if the presumed benefit from a decrease in HbA1c will counterbalance the potential harm due to weight gain.

Suggested Patient Labeling (Medication Guide)

[Drug] can cause an increase in body weight, in part by the way it works, converting the

⁵⁴ Memo of Saul Malozowski, M.D. to Solomon Sobel, M.D.; May 10, 1999.

⁵⁵ Pioglitazone Advisory Committee; April 23, 1999.

⁵⁶ Medical Officer's Review of Pioglitazone; June 23, 1999; pp. 10, 15.

glucose in your blood into fat in your fat cells. As long as you are taking [drug], you can expect to gain weight (an average of 2 to 12 pounds over 6 months, but it could be as much as 5% of your body weight). Weight gain may continue as long as you continue to take [drug].

Because long-term studies have not been conducted, it is not known how much weight you might eventually gain with long-term use of this drug, how this might affect the health of your heart, or how difficult it might be to lose this added weight once you stop taking [drug]. It is not known whether the decrease in your blood sugar would be beneficial enough to balance out the health problems of weight gain.

IID. EDEMA (See p. 34 of Appendix for current labeling)

Although the current labeling states that edema was seen in both the animal and human studies, there is no discussion of a mechanism that might cause this to occur. Without this knowledge, patients and physicians are left without a treatment strategy to prevent potentially harmful drug combinations such as combining a glitazone with a calcium channel blocker (see below).

Evidence Supporting A Labeling Change For Edema

Troglitazone: Edema was increased in incidence and severity in rats.⁵⁷

Rosiglitazone: Plasma volume increased in rats.⁵⁸

General: Both the glitazones and calcium channel blocking drugs inhibit the slow L-type calcium channel in cardiac and vascular smooth muscle. In vascular smooth muscle, these drugs decrease arteriolar resistance as a result of vasodilatation with a resultant decrease in blood pressure. Peripheral edema is an adverse event seen during treatment with calcium channel blockers as well as with glitazones^{59,60}; pulmonary edema has also occurred in patients on troglitazone.⁶¹

57 Pharmacology Review of Troglitazone; January 8, 1997; pp.11, 30.

58 Pharmacology Review of Rosiglitazone; January 5, 1995; p.14 and appendix Table 1.

59 Package Inserts and Medical and Pharmacology Reviews.

60 Gorson DM. Significant weight gain with rezulin therapy. Archives of Internal Medicine 1999;159:99.

61 Hirsch IB, Kelly J, Cooper S. Pulmonary edema associated with troglitazone therapy. Archives of Internal Medicine 1999;159:1811 and Koshida H, Shibata K, Kametani T. Pleuropulmonary disease in a man with diabetes who was treated with troglitazone. New England Journal of Medicine 1998;339:1400-1401.

Suggested Professional Labeling For Edema

Both the glitazones and calcium channel blocking drugs inhibit the slow L-type calcium channel in cardiac and vascular smooth muscle and both cause edema as an adverse reaction. [Drug] can cause peripheral edema. Pulmonary edema has also been reported for troglitazone, the glitazone on the market for the longest time. Patients should be monitored for fluid overload. [Drug] should not be used in patients with preexisting heart failure and/or who are on other drugs that block calcium channels.

Suggested Patient Labeling (Medication Guide)

[Drug] can cause accumulation of fluid or swelling in your legs, ankles, and lungs. You should let your doctor know if you notice swelling or have difficulty breathing. You should not take [drug] if you have congestive heart failure, or if you are taking a calcium channel blocker such as amlodipine or nifedipine.

II.E. ANEMIA (See p. 35 of Appendix for current labeling)

While anemia is listed in all three labels as an adverse event, there is no mention of its widespread occurrence in animals treated with these drugs nor any mention of a likely mechanism that emerged from animal studies: fat displacement of blood-forming cells in the bone marrow (see below). The current labeling attributes the decreases in red blood cells (RBCs) and white blood cells (WBCs) to increased plasma volume (a dilutional origin of anemia) although there is no evidence that is indeed the major or only cause. Furthermore, the labeling implies that anemia occurs during the first 4 to 8 weeks of treatment whereas, at least in the case of rosiglitazone, decreases in RBCs occurred after this time period.

Evidence Supporting A Labeling Change for Anemia**ANIMAL STUDIES**

Anemia is a common finding in rats, mice, and dogs; it appears to be the result of the conversion (in the bone marrow) of pre-adipocytes to adipocytes (a mechanism of drug action). In these species, femoral and sternal bone marrow had infiltrations of fat which consisted of varying degrees of vacuolization within the marrow cavity that displaced or compressed the existing marrow.⁶² Results from an *in vitro* study of the thiazolidinedione drug group "indicates that bone marrow stromal cells are a direct target for thiazolidinedione actions *in vivo*."⁶³

62 Pharmacology Review for Pioglitazone; June 30, 1999; pp.14, 16, 37.

63 Gimble JM, Robinson CE, Wu X, et al. Peroxisome proliferator-activated receptor-gamma activation by

HUMAN STUDIES

Anemia was also a common finding in clinical trials with all the glitazones.⁶⁴ Furthermore, decreases in white blood cells can occur by the same mechanism and have been reported in patients on both troglitazone and rosiglitazone.⁶⁵ An examination of bone marrow does not appear to have been done in any clinical trials. The glitazone package inserts state that anemia "may be related to increased plasma volume", but there is no evidence that this is the case.

Troglitazone: The Medical Officer expressed concern over decreases in hematological parameters stating that, "Troglitazone's effects on hematologic measures and liver injury remain safety issues."⁶⁶ White blood cell counts (as well as RBC) decreased (15 troglitazone-treated patients and one glyburide-treated patient had at least one absolute neutrophil count $<1,000/\text{mm}^3$).

Rosiglitazone: Two patients who developed anemia were withdrawn from clinical trials; another was continued although her hematocrit was only 20. In the monotherapy studies, 8 patients (0.3%) were withdrawn because of anemia, compared to 0.0% of patients on metformin, SFU [sulfonylurea], or placebo.⁶⁷

In a study with metformin, 0.5% of patients on metformin alone developed a low hematocrit compared to 3.5% on both metformin and rosiglitazone. These abnormalities generally developed after 60 days of treatment [vs. the label statement that they occurred in the first 4 to 8 weeks]. This delay in occurrence was true for monotherapy as well. The Medical Officer noted that, "The development of anemia when patients on metformin are treated with RSG is of concern and cannot be explained simply by expansion of vascular volume."⁶⁸

In a head-to-head study with glyburide, mean hemoglobin rose 0.01 g/dl in patients on glyburide but fell 0.48 g/dl and 0.98 g/dl in patients on 2 mg bid and 4 mg bid

thiazolidinediones induces adipogenesis in bone marrow stromal cells. *Molecular Pharmacology* 1996;50:1087-1094.

64 Package Inserts for Troglitazone, Rosiglitazone, and Pioglitazone.

65 Ibid.

66 Medical Officer's Review of Troglitazone; January 17, 1997; section 10.3.4; p.62.

67 Medical Officer's Review of Rosiglitazone; April 16, 1999; p.34.

68 Ibid; p.36.

rosiglitazone after 52 weeks of treatment.⁶⁹

Pioglitazone: Five out of 599 patients on pioglitazone had decreases in hematocrit of >10%; one female dropped 26% (from 35 to 26); no significant changes were mentioned for the placebo group.⁷⁰ The decreases in hematocrit were greater when pioglitazone was combined with metformin (mean drop of 1.2 combined vs. 0.38 alone).⁷¹

SUMMARY: The labels do mention anemia under "Laboratory Abnormalities" but dismiss its significance; the possibility of a drug action on bone marrow cells through adipocyte differentiation is never mentioned. In addition, even though the Medical Officer noted that, "There should be some specific instruction about what to expect and what to do" concerning the increased rate of anemia when metformin is combined with rosiglitazone⁷², the label states that there is no increase in anemia with this combination.

Suggested Additions and Corrections to the Professional Labeling for Anemia
Dose-related decreases in hemoglobin, hematocrit, RBC, and WBC counts have been observed in patients on [drug]. One possible cause is fatty infiltration of the bone marrow (by conversion of pre-adipocytes to adipocytes, a mechanism of drug action). Decreases in RBC and WBC have been reported both early and late in treatment; thus, periodic monitoring is recommended. The incidence of anemia was increased in patients taking both metformin and rosiglitazone; decreases in hematocrit were bigger when metformin was combined with pioglitazone.

Suggested Patient Labeling (Medication Guide)

Decreases in red blood cells and white blood cells may occur while taking this drug. Your doctor should run blood tests periodically for the first year to see if this is occurring. Metformin (Glucophage) and rosiglitazone taken together increase the chance of anemia occurring. Metformin and pioglitazone taken together produced larger drops in red blood cell counts.

⁶⁹ Ibid; p.18.

⁷⁰ Medical Officer's Review of Pioglitazone; June 23, 1999; p.40.

⁷¹ Ibid; p.40.

⁷² Medical Officer's Review of Rosiglitazone; April 16, 1999; p.40.

IIF. BLOOD PRESSURE LOWERING (See p. 35 of Appendix for current labeling)

There is no information in any of the current labels on lowering of blood pressure. Most of the available clinical information comes from studies on troglitazone since that appears to be the only drug where blood pressure was routinely monitored. This is unacceptable since the drug has known calcium channel blocking effects. However, even this information was not included in the label nor was related information from animal studies.

**Evidence Supporting Labeling Change For Blood Pressure Lowering
ANIMAL STUDIES**

Pioglitazone: A study on the mechanism of blood pressure lowering in rats led the authors to conclude that, "... PIO has a direct vascular effect that appears to be mediated at least in part by inhibition of agonist-mediated calcium uptake by vascular smooth muscle [and] ... may contribute to the blood pressure-lowering actions of PIO".⁷³ Blood pressure does not seem to have been measured with pioglitazone.

HUMAN STUDIES

Troglitazone: The Medical Officer noted that, "Statistically significant decreases from baseline in systolic and diastolic blood pressure were observed at Week 24 for both troglitazone and glyburide treatment groups. At Week 48, however, only troglitazone-treated patients showed a decrease in diastolic BP. ... that was statistically significant" (mean decreases of 5.7 mm Hg)⁷⁴ or -6.5 mm.⁷⁵

The Troglitazone Study Group found that the reduction in blood pressure in patients on troglitazone was pronounced and statistically significant: "Similar changes were not observed in the glyburide patients." They speculated that, "*the reduction in blood pressure seen with troglitazone treatment could be attributed to a direct effect mediated through calcium channel blocker activity as has been observed with pioglitazone treatment, another member of the thiazolidinedione family*" (italics added).⁷⁶

73 Buchanan TA, Meehan WP, Jeng YY et al. Blood pressure lowering by pioglitazone. Journal of Clinical Investigation 1995;96:354-360.

74 Medical Officer's Review of Troglitazone; January 17, 1997; p.52.

75 Ghazzi MN, Perez JE, Antonucci TK, et al. Cardiac and glycemic benefits of troglitazone treatment in NIDDM. Diabetes 1997;46:433-439.

76 Ibid..

Suggested Professional Labeling: [Drug] can cause a decrease in blood pressure that has been suggested to be a direct effect mediated through its calcium channel blocking activity. Calcium channel blockers lower blood pressure by causing a decrease in peripheral vascular resistance. Monitoring of blood pressure is recommended.

Suggested Patient Labeling (Medication Guide): [Drug] can cause a decrease in your blood pressure. Your doctor should check your blood pressure before you start using [drug] and when you have your office visits. If you are taking other drugs for lowering blood pressure, you should get more frequent follow-up of your blood pressure. Let your doctor know if you experience dizziness or fainting.

II. PLASMA LIPIDS (See p. 36 of Appendix for current labeling)

There are statements about increased lipid levels in the current label, but most of them are very general in nature.

Evidence Supporting Labeling Change For Changes In Lipids

Troglitazone: Total, LDL, and HDL cholesterol were increased in patients treated with 200 or 400 mg/day, although triglycerides did not differ between groups.⁷⁷

Rosiglitazone: The statistical reviewer provided the most comprehensive analysis of lipid changes for a glitazone: she concluded that total cholesterol, LDL, and LDL/HDL increased significantly in patients on rosiglitazone (compared to placebo, glibenclamide, and metformin). Patients with the lowest baseline LDL (<130 mg/dl) had the largest increases (23 to 32%).⁷⁸

In multiple places in the Medical Officer's review, concern over potentially adverse lipid effects was evident: "[rosiglitazone] is associated with increases in total cholesterol, HDL, and LDL in comparison to patients not receiving [rosiglitazone]." "Also, these trials were too short to exclude damage resulting from the long term effects of weight gain and hyperlipidemia."⁷⁹ "... RSG tends to cause HDL/LDL cholesterol and VLDL

⁷⁷ Medical Officer's Review of Troglitazone NDA; January 17, 1997; p.27.

⁷⁸ Statistical Review of Rosiglitazone; May 11, 1999; pp27-30.

⁷⁹ Medical Officer's Review of Rosiglitazone; April 16, 1999; p.37.

to go in the wrong direction with respect to cardiac risk."⁸⁰

Pioglitazone: Total, LDL, and HDL cholesterol levels rose in all groups treated with 7.5 to 45 mg/day for six months; triglyceride levels fell.⁸¹ In a 4-month study using a 30 mg/day dose, HDL rose and triglycerides fell while changes in total and LDL cholesterol were not significant.⁸²

Suggested Professional Labeling for lipids (Rosiglitazone): Patients may have an increase in total cholesterol, LDL, and LDL/HDL. Lipid levels should be monitored at baseline and periodically thereafter.

Suggested Patient Labeling (Medication Guide for Rosiglitazone): Your doctor will test your blood before you start taking [drug] to see if your cholesterol levels are normal. This test will be repeated during your first year of therapy because [drug] can adversely affect your cholesterol levels.

III. HORMONE LEVELS

Monkeys given rosiglitazone become anovulatory and subsequently amenorrheic as a result of the inhibition of a key enzyme in the steroid synthetic pathway (3-beta-hydroxysteroid dehydrogenase) that converts pregnenolone to progesterone.⁸³ There is no information in the label about the inhibition of this enzyme which might cause women to become anovulatory.

Suggested Professional Labeling: The glitazones inhibit a key enzyme in the steroid synthesis pathway, 3-beta-hydroxysteroid dehydrogenase, that converts pregnenolone to progesterone.⁸⁴ As a result of this action, monkeys became amenorrheic when treated with Avandia (the only drug examined for this effect). Premenopausal women need to be aware of this possibility.

⁸⁰ Ibid; p.39.

⁸¹ Medical Officer's Review of Pioglitazone; June 23, 1999; p.10.

⁸² Ibid; p.19.

⁸³ Dr. Patrick Wier; Advisory Committee on Rosiglitazone, April 22, 1999.

⁸⁴ Ibid.

Suggested Patient Labeling (Medication Guide)

[Drug] can cause the ovaries to stop producing a hormone that is needed for normal menstruation and fertility. If you plan to become pregnant, you should not take this drug.

III. PEDIATRIC USE

The glitazone labels state: "There are no data on the use of [drug] in patients under 18 years of age; therefore, use of [drug] in pediatric patients is not recommended." This statement is inadequate. The use of glitazones in children should be contraindicated because of the unknown potential for hepatotoxicity, effects on steroidogenesis, and fat deposition.

Hepatic toxicity: SmithKline Beecham stated (in a letter to the FDA dated April 1, 1999 concerning rosiglitazone) that because the magnitude of hepatotoxicity will "only become fully apparent with postmarketing experience" and because according to "the final pediatric rule, studies should not begin in pediatric patients until after the safety profile of the drug is well established through postmarketing experience", that initiation of pediatric studies would not begin at that time. If the sponsor is unwilling to administer the drug to children even in the controlled setting of a clinical trial, the drug should be contraindicated in children in routine clinical practice.

Steroidogenesis: Monkeys given rosiglitazone become anovulatory and subsequently amenorrheic as a result of the inhibition of a key enzyme in the steroid synthetic pathway (3-beta-hydroxysteroid dehydrogenase) that converts pregnenolone to progesterone.⁸⁵ For this reason, we have great concern in giving a drug in this class to young women who might become anovulatory. Unfortunately, hormone levels have not been measured nor has adrenal steroidogenesis been studied in humans.

Body composition: A member of the Advisory Committee brought up the "concern about its [rosiglitazone] use in adolescents because of the possibility of increasing fat deposition that may not disappear . . .".⁸⁶ Pediatric patients would be increasing their permanent adipose tissue putting them at increased diabetic risk and for a much longer period of time than adults.

⁸⁵ Dr. Patrick Wier; Advisory Committee on Rosiglitazone, April 22, 1999.

⁸⁶ Dr. Jules Hirsch; Ibid.

Suggested Professional and Pediatric Labeling:

The use of [drug] in children is contraindicated because of the unknown potential for hepatotoxicity, fat deposition, and effects on steroidogenesis.

IV. LONG-TERM USE (UNDER "INDICATIONS AND USAGE")**Suggested Professional Labeling.**

While [drug] has been shown to reduce glucose and HbA1c levels, there is no evidence that lowering glucose levels with this drug will reduce the risks of microvascular or macrovascular disease or decrease mortality in patients with type 2 diabetes.

Special Warning On Increased Risk Of Cardiovascular Morbidity and Mortality

A review of trials in hypertensive patients, which included type 2 diabetics taking a calcium antagonist drug, led to the conclusion that there was an increased risk for cardiovascular events in patients taking the calcium antagonist drugs.⁸⁷ Since the glitazones have calcium antagonist activity as one of their actions, using glitazones in hypertensive type 2 diabetics may put this group at increased risk of adverse cardiovascular events. Adverse event data reported to the FDA include heart failure in 56 troglitazone patients (over an 18 month period)⁸⁸ and 5 rosiglitazone patients (over a 4 month period).⁸⁹

Furthermore, vasoactive effects of troglitazone have led to speculation that the vasodilator and blood pressure lowering effects could be disadvantageous if dilating the precapillary resistance arteries (allowing transmission of arterial blood pressure to the capillary circulation) accelerated microangiopathy.⁹⁰

Suggested Patient Labeling (Medication Guide)

Although [Drug] may lower glucose levels in your blood, no one knows if this will reduce your chance for developing problems with your heart, eyes, nerves, or kidneys or effect how long you live.

87 Abernethy DR, Schwartz JB. Calcium-antagonist drugs. New England Journal of Medicine 1999;341:1447-1457.

88 AERS of the FDA collected between November 1997 and June 1998.

89 AERS of the FDA collected between June and October 1999.

90 Walker AB, Naderali EK, Chattington PD, et al. Differential vasoactive effects of the insulin sensitizers rosiglitazone (BRL 49653) and troglitazone on human small arteries in vitro. Diabetes 1998;47:810-814.

V. GENERAL COMMENTS FOR LABEL

Table of Adverse Effects: These tables should include events with an incidence of equal to or greater than 1 % (as opposed to 5% now). At a minimum, adverse events that are known to be associated with drug use in controlled clinical trials should be included in the table even if they occur less frequently than in 5% of patients.

SUMMARY

In summary, we have major concerns on the relative efficacy and safety of the glitazones. We have described in this petition what we believe to be class effects that affect the physician's ability to properly prescribe and to monitor safety in patients. These issues have either not been mentioned at all or have not been adequately addressed in the label. The label needs to be revised immediately.

ENVIRONMENTAL IMPACT STATEMENT

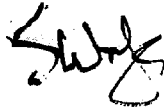
Nothing requested in this petition will have an impact on the environment.

CERTIFICATION

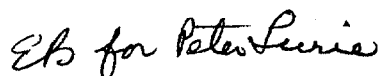
We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

We look forward to a prompt response to this petition.

Sincerely,



Sidney M. Wolfe, M.D.
Director, Public Citizen's Health Research Group



Peter Lurie, M.D.
Deputy Director, Public Citizen's Health Research Group



Elizabeth Barbehenn, Ph.D.
Research Analyst, Public Citizen's Health Research Group

APPENDIX (CURRENT LABELING) EFFICACY ISSUES

GLITAZONES ARE LESS EFFECTIVE AS MONOTHERAPY IN DIABETIC PATIENTS PREVIOUSLY TREATED WITH ANOTHER ORAL ANTI-DIABETIC DRUG

Current Glitazone Labeling (Under "Clinical Studies")		
Troglitazone91	Rosiglitazone92	Pioglitazone93
"...patients who switched from a sulfonylurea to Rezulin monotherapy also demonstrated increases in FSG* and HbA1C."	"Patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin and who were switched to monotherapy with Avandia demonstrated loss of glycemic control, as evidenced by increases in FPG and HbA1c."	"...however, for the previously-treated group, washout from previous anti-diabetic medication resulted in deterioration of glycemic control and increases in HbA1c and FBG.**" "For many previously-treated patients, HbA1c and FBG had not returned to screening levels by the end of the study."

*FSG Fasting Serum Glucose; **FBG fasting blood glucose (blood sugar level)

GLITAZONES ARE NOT AS EFFECTIVE AS OLDER DRUGS WHEN USED ALONE IN REDUCING BLOOD SUGAR AND HbA1c

Current Glitazone Labeling (comparative)		
Troglitazone	Rosiglitazone	Pioglitazone
No information in label	See Fig. 2 in label	No comparative study was done.

91 Rezulin (troglitazone) Professional Product Labeling at www.rezulin.com/ obtained 9/22/99.

92 Avandia (rosiglitazone) Professional Product Labeling at www.avandia.com obtained 9/22/99.

93 Actos (pioglitazone) Professional Product Labeling at www.actos.com obtained 9/22/99.

APPENDIX SAFETY ISSUES

1) ALT ELEVATIONS

Current Glitazone Labeling (Under "Laboratory Abnormalities")		
Troglitazone	Rosiglitazone	Pioglitazone
<p>Black box warning at beginning of label: "Hepatotoxicity Severe idiosyncratic hepatocellular injury has been reported during marketed use (see ADVERSE REACTIONS). The hepatic injury is usually reversible, but very rare cases of hepatic failure, leading to death or liver transplant, have been reported."</p> <p>Under "lab abnormalities": During all clinical studies in North America, a total of 48 of 2510 (1.9%) Rezulin-treated patients and 3 of 475 (0.6%) placebo-treated patients had ALT levels greater than 3 times the upper limit of normal." "Twenty of the rezulin-treated and one of the placebo-treated patients were withdrawn from treatment. Two of the 20 Rezulin-treated patients developed jaundice; one of these patients had a liver biopsy which was consistent with an idiosyncratic drug reaction."</p>	<p>"In clinical studies in 4598 patients treated with Avandia encompassing approximately 3600 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevated ALT levels."</p> <p>(plus under PRECAUTIONS, there is information on ALT measurements, lack of clear causality, etc.)</p>	<p>"During placebo-controlled clinical trials in the U.S., a total of 4 of 1526 (0.26%) ACTOS-treated patients and 2 of 793 (0.25%) placebo-treated patients had ALT values greater or equal to 3 times the upper limit of normal. All patients with follow-up values had reversible elevations in ALT."</p> <p>(plus under PRECAUTIONS, there is information on ALT measurements, lack of clear causality, etc.)</p>

APPENDIX

2) EFFECTS ON THE HEART

Current Glitazone Labeling (Under "Precautions")		
Troglitazone	Rosiglitazone	Pioglitazone
<p>"Heart enlargement without microscopic changes has been observed in rodents at exposures of parent compound and active metabolite exceeding 7 times the AUC of the 400 mg human dose. . ."</p> <p>"Increased heart weights without microscopic changes were observed in mice and rats treated for up to 1 year at exposure (AUC) of parent and active metabolite exceeding 7 times the human AUC at 400 mg/day." "In the lifetime carcinogenicity studies, microscopic changes were noted in the hearts of rats.... In control and treated rats, microscopic changes included myocardial inflammation and fibrosis and karyomegaly of atrial myocytes. ...at twice the AUC of the 400 mg human dose."</p>	<p>"In preclinical studies, thiazolidinediones, including rosiglitazone, cause plasma volume expansion and pre-load-induced cardiac hypertrophy. Two ongoing echocardiography studies in patients with type 2 diabetes (a 52-week study with Avandia 4 mg twice daily [n=86] and a 26-week study with 8 mg once daily [n=90], have shown no deleterious alteration in cardiac structure or function."</p>	<p>"In preclinical studies, thiazolidinediones, including pioglitazone, cause plasma volume expansion and pre-load-induced cardiac hypertrophy (see PRECAUTIONS, Animal Toxicology)." "In clinical trials that excluded patients with New York Heart Association Class III and IV cardiac status, no increased incidence of serious cardiac adverse events potentially related to volume expansion (e.g., congestive heart failure) was observed."</p>

3) WEIGHT GAIN (GLUCOSE CONVERSION INTO FAT)

Current Glitazone Labeling (Under "Pharmacodynamics and Clinical Effects")		
Troglitazone	Rosiglitazone	Pioglitazone
<p>No mention of weight gain in label.</p>	<p>"Reduction in hyperglycemia was associated with increases in weight. In the 26-week clinical trials, the mean weight gain in patients treated with Avandia was 1.2 kg (4 mg daily) and 3.5 kg (8 mg daily) when administered as monotherapy and 0.7 kg (4 mg daily) and 2.3 kg (8 mg daily) when administered in combination with metformin. A mean weight loss of about 1 kg was seen for both placebo and metformin alone in these studies."</p>	<p>"In all clinical trials, a reduction in HbA1c was accompanied by increased body weight in ACTOS-treated patients in a dose-related manner. The change in average weight in US placebo-controlled monotherapy trials ranged from 0.5 kg to 2.8 kg for ACTOS-treated patients and -1.3 kg to -1.9 kg for placebo-treated patients."</p>

APPENDIX

4) EDEMA

Current Glitazone Labeling (Under "Precautions")		
Troglitazone	Rosiglitazone	Pioglitazone
<p>"In animal studies, troglitazone treatment was associated with increase of 6% to 15% in plasma volume. In a study of 24 normal volunteers, an increase in plasma volume of 6% to 8% compared to placebo was observed. . ."</p> <p>"No increased incidence of adverse events potentially related to volume expansion (eg, congestive heart failure) have been observed during controlled clinical trials."</p>	<p>"In preclinical studies, thiazolidinediones, including rosiglitazone, cause plasma volume expansion and pre-load-induced cardiac hypertrophy."</p> <p>"Avandia should be used with caution in patients with edema. In a clinical study in healthy volunteers who received 8 mg once daily for 8 weeks, there was a statistically significant increase in median plasma volume (1.8 ml/kg) compared to placebo."</p> <p>"In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with Avandia."</p>	<p>"ACTOS should be used with caution in patients with edema. In double-blind clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with ACTOS (see ADVERSE REACTIONS)."</p>

APPENDIX

5) ANEMIA

Current Glitazone Labeling (Under "Precautions" and "Adverse Reactions")

Troglitazone	Rosiglitazone	Pioglitazone
<p>Under "Precautions": "Across all clinical studies, hemoglobin declined by 3% to 4% in troglitazone-treated patients compared with 1% to 2% in those treated with placebo. White blood cell counts also declined slightly in troglitazone-treated patients compared to those treated with placebo. These changes occurred within the first four to eight weeks of therapy. Levels stabilized and remained unchanged for up to two years of continuing therapy. These changes may be due to the dilutional effects of increased plasma volume and have not been associated with any significant hematologic clinical effects."</p> <p>Under "Adverse Reactions": "Small decreases in hemoglobin, hematocrit, and neutrophil counts (within the normal range) were more common in Rezulin-treated patients than placebo-treated patients and may be related to increased plasma volume observed with Rezulin treatment. Hemoglobin decreases to below the normal range occurred in 5% of Rezulin-treated and 4% of placebo-treated patients."</p>	<p>Under "Precautions": "Across all controlled clinical studies, decreases in hemoglobin and hematocrit (mean decreases in individual studies up to ≤ 1.0 gram/dL hemoglobin and up to $\leq 3.3\%$ hematocrit) were observed for both Avandia alone and in combination with metformin. The changes occurred primarily during the first 4 to 8 weeks of therapy. . ."</p> <p>"White blood cell counts also decreased slightly in patients treated with Avandia. Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with Avandia. The observed changes may be related to the increased plasma volume observed with treatment with Avandia and have not been associated with any significant hematologic clinical effects"</p> <p>Under "Adverse Reactions": "The time course and magnitude of decreases were similar in patients treated with a combination of Avandia and metformin or monotherapy."</p>	<p>Under "Precautions" and "Adverse Reactions": "ACTOS may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in ACTOS-treated patients. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with ACTOS therapy and have not been associated with any significant hematologic clinical effects."</p>

6) BLOOD PRESSURE LOWERING

Current Glitazone Labeling		
Troglitazone	Rosiglitazone	Pioglitazone
No information	No information	No information

APPENDIX

7) PLASMA LIPIDS

Current Glitazone Labeling (Under "Clinical Pharmacology")		
Troglitazone	Rosiglitazone	Pioglitazone
"In clinical trials of Rezulin, an increase in LDL (up to 13%), HDL (up to 16%), and total cholesterol (total-C) (up to 5%) occurred while total-C/HDL and LDL/HDL ratios did not change. The increase in total cholesterol is due to the increase in HDL and LDL cholesterol."	"Avandia as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids."	"Overall, patients treated with ACTOS had mean decreases in triglycerides, mean increases in HDL cholesterol and no consistent mean changes in LDL and total cholesterol."

**CITIZEN'S PETITION TO IMMEDIATELY REQUIRE CLASS LABELING
FOR THE DIABETES DRUGS TROGLITAZONE (REZULIN),
ROSIGLITAZONE (AVANDIA) AND PIOGLITAZONE (ACTOS)**

Fig. 4 TROGLITAZONE (Study #031)

Oral-Agent Pretreatment

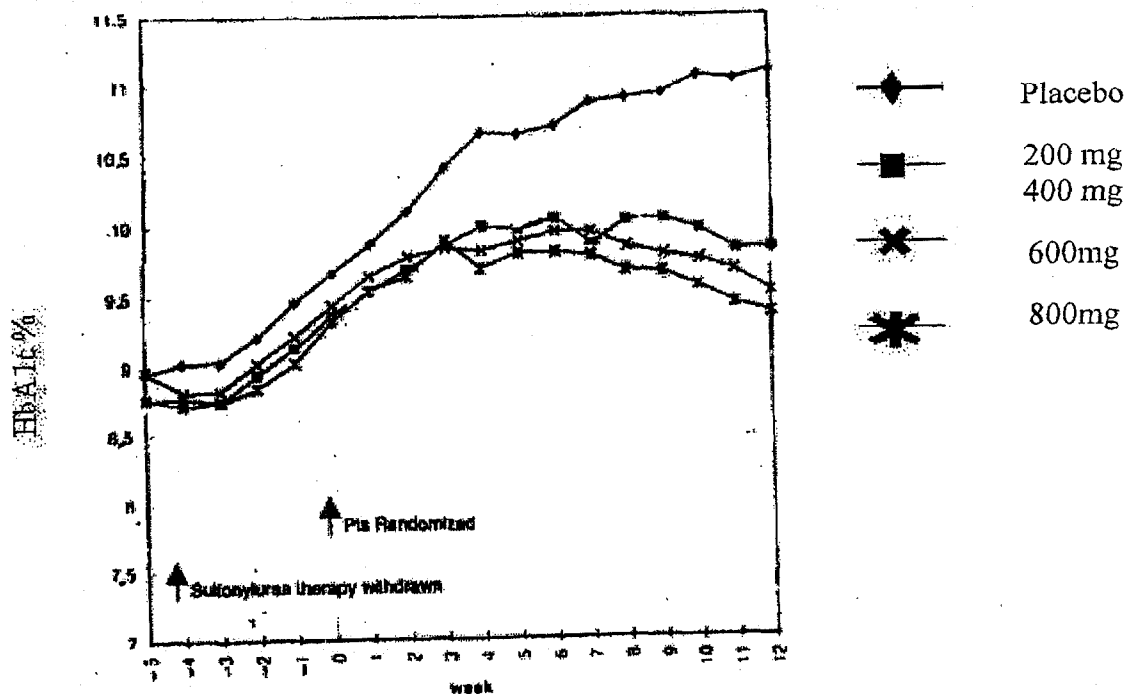


Fig. 5 TROGLITAZONE (Study #055)

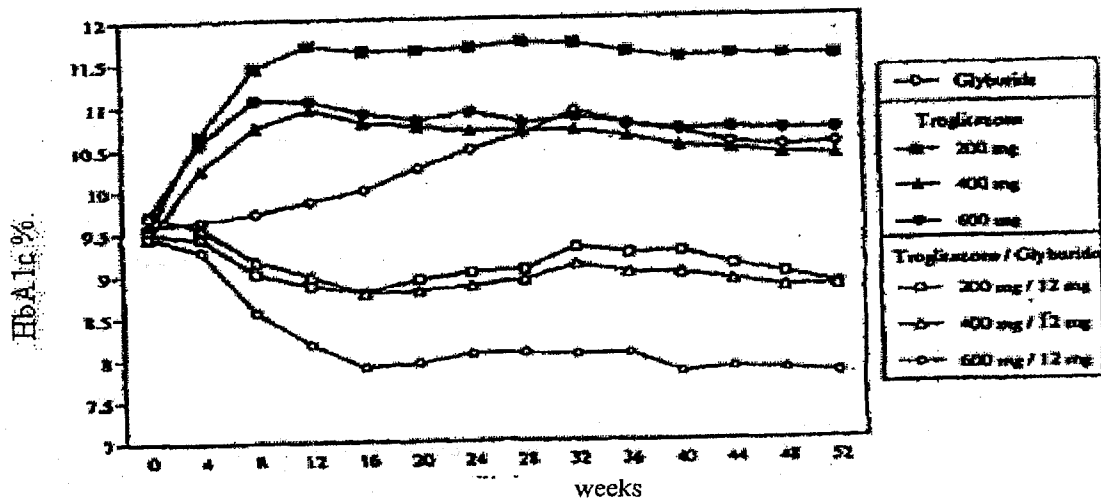
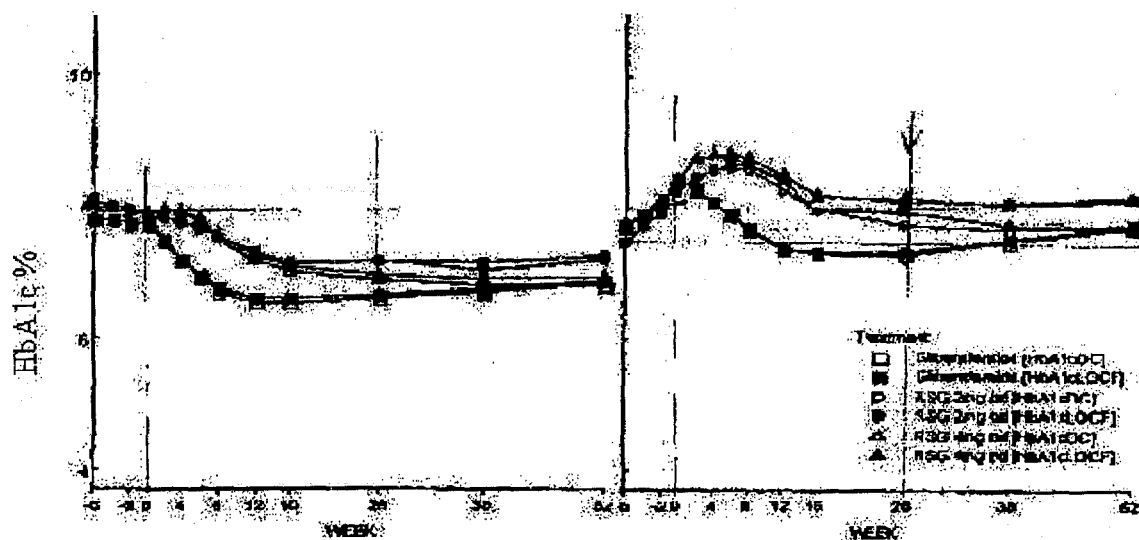


Fig.6 ROSIGLITAZONE (Study #020)

Prior Anti-diabetic Medication

NO

YES

**Fig. 7 ROSIGLITAZONE (Study #024)**

Prior Anti-Diabetic Medication

NO

YES

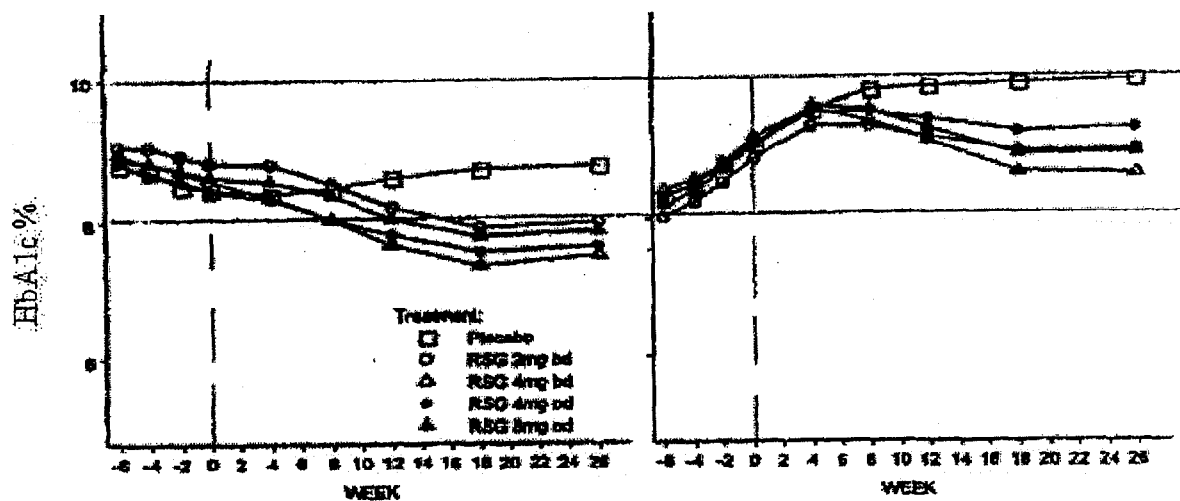


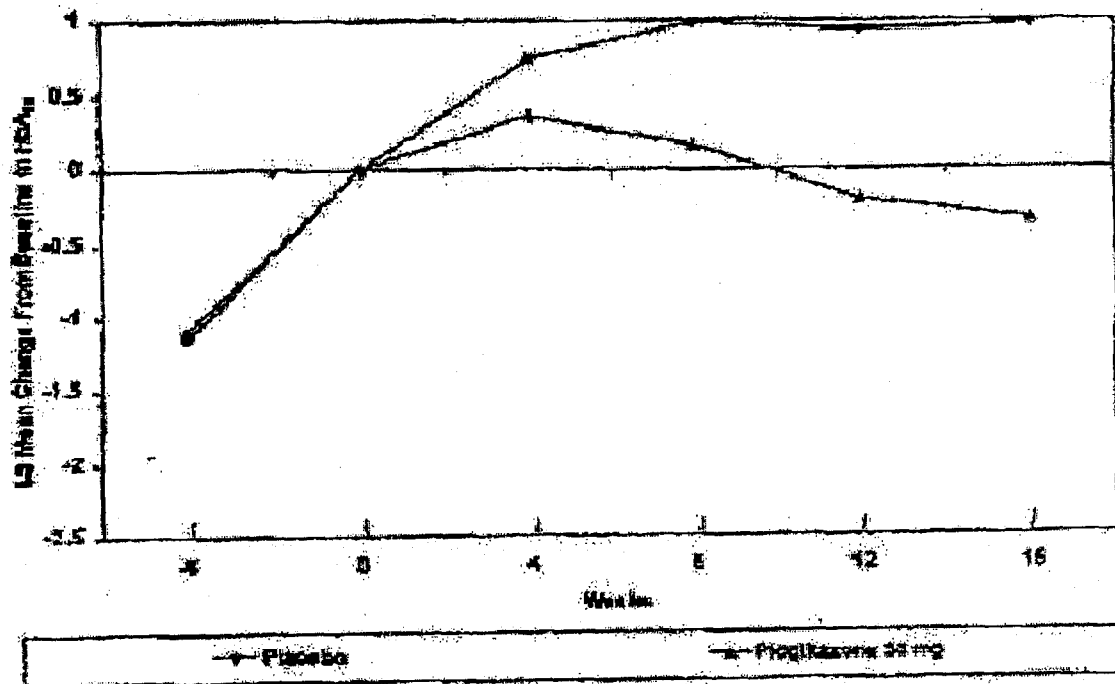
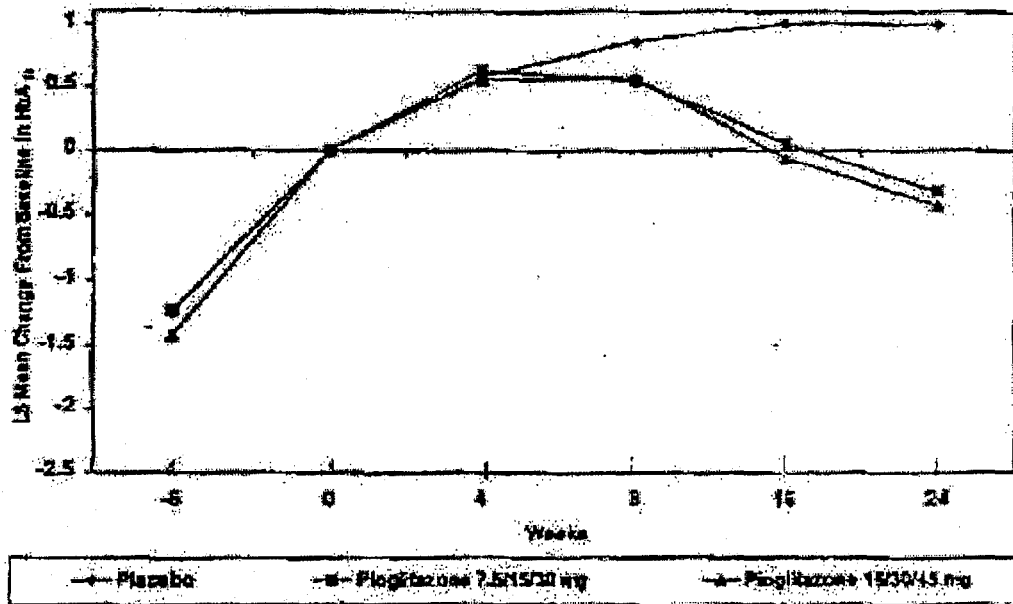
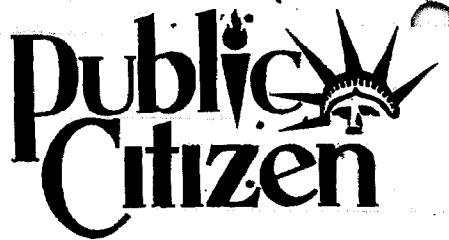
Fig. 8 PIOGLITAZONE (Study #026)

Fig. 9 PIOGLITAZONE (Study #012)



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Joan Claybrook, President

FAX MESSAGE

From: Health Research Group

To: Jane Henney, MD

Date: 3/7/00

Fax No. 301-443-3100

No. of pages, including cover 41

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Ralph Nader, Founder

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TO: JANE E HENNEY HF-1

FROM: SIDNEY M WOLFE, PUBLIC CITIZEN'S HEALTH RESEARCH GROUP
PETER LURIE, PUBLIC CITIZEN
ELIZABETH BARBEHENN, PUBLIC CITIZEN'S HEALTH RESEARCH GROUP

SYNOPSIS: CITIZEN'S PETITION TO IMMEDIATELY REQUIRE CLASS LABELING FOR THE
DIABETES DRUGS TROGLITAZONE (REZULIN), ROSIGLITAZONE (AVANDIA)
AND PIOGLITAZONE (ACTOS).

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